The
Journal of Infectious Diseases

PUBLISHED BY THE MEMORIAL INSTITUTE FOR INFECTIOUS DISEASES

VOL. 10 *May 1912* No. 3

THE CHANGES IN INFLUENZAL PNEUMONIA.*

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During epidemics of influenza, pneumonia occurs in about 5 per cent of the cases and the mortality ranges from 15 to 50 per cent. Before Pfeiffer's discovery of the influenza bacillus it had been noted that pneumonia was common during the epidemic periods, and efforts were made to determine its cause. Chiefly streptococci and pneumococci were found in the lungs and though by some they were considered the cause, by most writers they were thought to be secondary invaders. After Pfeiffer's work[1] the problem resolved itself into a correlation of bacteriological results and anatomic alterations. Pfeiffer declared that the influenza bacillus could be a cause of pneumonia, since it was found in some cases practically pure in the lung parenchyma. Anatomically many of these pneumonias were entirely catarrhal and seemed to correspond to the ordinary lobular pneumonia. Leichtenstern[2] makes the following statement concerning this type of pneumonia: "The description of influenza pneumonia is but a repetition of what we have long known regarding the anatomic course of a pure catarrhal

* Received for publication February 17, 1912.

[1] *Ztschr. f. Hyg. u. Infektionskr.*, 1893, 13, p. 357.

[2] Nothnagel, *Encyclopedia of Practical Medicine*, 1905, p. 611.

pneumonia. As the inflammation proceeds from the bronchi into the pulmonary tissues there arise, as always under such conditions, lobular areas of inflammation which either remain separated by tissues containing air or coalesce to secondary lobar areas whose origin from lobular foci can still be recognized. The cut surface is quite smooth and on pressure drops of yellow pus ooze from the severed bronchi. Microscopically the whole appearance is one of catarrhal suppuration in optima forma. The alveolar lumina and septa, as well as the peribronchial connective tissue, are so infiltrated with round cells that apparently the lung structure is entirely obliterated. In the alveoli surrounding these purulent infiltrations, besides containing round cells, the alveolar epithelium is much swollen. In preparations stained by Weigert's method the absence of fibrin (or its occurrence at most in traces) in the areas of infiltration is very evident."

This lobular type of pneumonia, however, was by no means the only form that complicated influenza. According to many writers the croupous form often occurred and was noted by some to be more common than the lobular (Birch-Hirschfeld, Naunyn, Rollinger, Marchand, Weichselbaum, Menetrier). The question became complicated apparently for two reasons: first, epidemics of genuine lobar pneumonia existed simultaneously with the epidemics of influenza, as was noted, for instance, by Weichselbaum in Vienna; second, because atypical and mixed forms of pneumonia commonly occurred. These latter varied markedly both clinically and anatomically and naturally were described very differently by different observers.[1] Thus there arose much confusion and difference of opinion, and many points concerning the true character of influenza pneumonia remained unsettled. Quoting from Leichtenstern again: "The reason for this difference of opinion is obvious. It depends upon the fact that at the bedside it is often impossible to differentiate between the two forms (lobular and lobar), and that the anatomic differential diagnosis is by no means always easy and certain. It is in influenza especially that transition forms of lobular and lobar infiltration occur whose anatomic character, whether catarrhal or croupous, is often extremely difficult either macro-

[1] Kuskow, "Pathologische Anatomie der Influenza," *Arch. f. Path. Anat.*, etc., 1895, 139, p. 406.

scopically or microscopically to recognize." The cause of these atypical catarrhal-croupous or mixed pneumonias, while not entirely clear, would seem to be the existence of mixed and secondary infections, for in such cases pneumococci or streptococci or both, with or without influenza bacilli, are not infrequently found. It should be stated that much of our data on influenza were obtained during the epidemic of 1889–90 and were almost purely anatomic in character, the bacteriologic studies at this period being incomplete. Since that epidemic the influenza question has been further confused on account of the fact that the terms "influenza" and "grippe" have been applied without bacteriological examinations to almost every clinical condition that bears any resemblance to true influenza, including the common epidemics of colds. Many of these infections we now know are caused not by the influenza bacillus, but by streptococci, pneumococci, *M. catarrhalis*, etc. The confusion regarding the etiology of influenza or grippe naturally was extended to the complicating pneumonias, and consequently the term influenzal pneumonia was applied to lesions with which the influenza bacillus had nothing to do.

The above statements are sufficient, I think, to indicate the difficulty of obtaining from the literature a clear conception of influenzal pneumonia and to give an idea of the confusion that exists concerning this disease. I have therefore been led to present some data on this subject which have been acquired from the study of a number of cases of influenzal meningitis[1] associated with pneumonia. Five cases came to autopsy. In four, in addition to the pure influenzal meningitis, were definite pneumonic lesions in which the influenza bacillus occurred nearly pure or as the predominating organism. The respiratory tract also, as would appear from the clinical histories, was the probable primary seat and the atrium of infection. In three instances the influenza bacillus was found in the heart's blood practically pure. There can be no doubt, therefore, that the cases were severe infections with the influenza bacillus and that the alterations in the lungs may be regarded as typical of influenzal pneumonia. A somewhat detailed description of these lesions is therefore given and the results are

[1] These cases of meningitis were reported in *Am. Jour. Dis. Children*, 1911, 1, p. 249.

compared with the observations of others on pneumonia associated with influenza meningitis and also on bronchopneumonia of other origin, especially that complicating the respiratory type of influenza.

The five cases examined were all children one year of age or less. Clinically a definite history of "colds," preceding the meningeal trouble, was obtained in four cases, and bronchitis or bronchopneumonia was recognized usually a short time before the meningeal symptoms and several days before death. The pneumonia was manifested by fever, harsh breath sounds, areas of dulness, fine and coarse rales, etc. In general, both clinically and pathologically, the cases are very similar and individual statements or descriptions, except in certain instances, need not be given.

From a careful review of the alterations in the lungs the following account is written. Macroscopically in four of the five children there are definite pneumonic regions. Both lungs are affected about equally, and the consolidated portions occur chiefly in the lower lobes and in the posterior parts. In two cases the upper lobes are likewise involved. In no instance are there pleural adhesions either between the lobes or in the pleural cavities. Over the consolidated portion of the lungs as a rule the pleura is granular and covered by a thin delicate layer of fibrin. There is no fluid in the pleural cavities in any case. In one instance small hemorrhages are seen just beneath the pleura.

On section the lungs are moist, but not strikingly bloody, even in the lower parts. The distribution of the regions of consolidation is similar in most cases and the irregular lobulations are easily seen. The pleural surface is distinctly elevated over the involved parenchyma and here and there, especially around the consolidated lung tissue, are often bluish, depressed regions of atelectasis, variable in size. Single consolidated lobules may be found, but in two cases they have coalesced, forming consolidated masses one to several centimeters across in the posterior and lower parts of the lung near the hilus. These consolidated parts sink in water and are absolutely airless. The surfaces made by cutting them are smooth and do not present the granular appearance of lobar pneumonia. The color is reddish or yellowish gray. This pneumonic lung tissue is often sharply marked off from the surrounding regions, especially

by the fibrous septa, and for the most part lies located immediately under the pleura.

Adjacent and usually anterior to these confluent pneumonic regions are others less completely solidified and having a mottled red and gray color. This mottling, as seen on the cut surface, is due to small solid gray areas one or two millimeters across, separated by slightly darker zones. Such regions are conspicuous on section of the lungs and are far more extensive than the completely confluent regions. From their centers, on slight pressure, there exude small droplets of pus. About these mottled regions, especially anterior and extending well forward sometimes to the anterior margin of the lung, the tissue contains much more air, does not sink in water, and is darker red in color; here are only a few gray points representing small bronchi surrounded by a narrow zone of pneumonic lung. In places along the anterior margin the lung tissue is sometimes slightly emphysematous, but this is not constant. Fibrin plugs are not noted in the bronchi. In the larger bronchi abundant mucinous purulent fluid is always found and the mucosa is diffusely red. This condition extends into the trachea and involves the upper respiratory tract generally.

For microscopic examination pieces were obtained from different parts of the lungs, sectioned in paraffin and stained with hematoxylin and eosin, Van Gieson stain, Weigert's elastic fiber stain, polychrome methylene blue, methyl green-pyronin mixture, dilute carbofuchsin, and Giemsa stain.

In the consolidated lung tissue as a rule the alveoli and bronchial tubes are filled with a rich exudate. At the margins of the consolidated portions it is evident that the process is essentially lobular because the infiltrated regions surround the bronchi and are separated by tissue which contained air during life. In places a branching distribution of the pneumonic areas suggests the successive invasion of the various parts of the lung along the bronchial tubes. In some sections there are large bronchi with intense mural infiltration surrounded by a narrow marginal zone of pneumonic acini. The epithelial cells lining the bronchial tubes are often desquamated, lying free in the lumen singly or in small clusters. They may show evidence of marked degeneration. In the epithelial

layer may be seen polymorphonuclear leukocytes and an occasional plasma cell, apparently fixed while in the act of wandering outward into the lumen. Accumulation of leukocytes just under the epithelium is not noted in the sections. The small blood vessels and capillaries in the wall are usually intensely hyperemic.

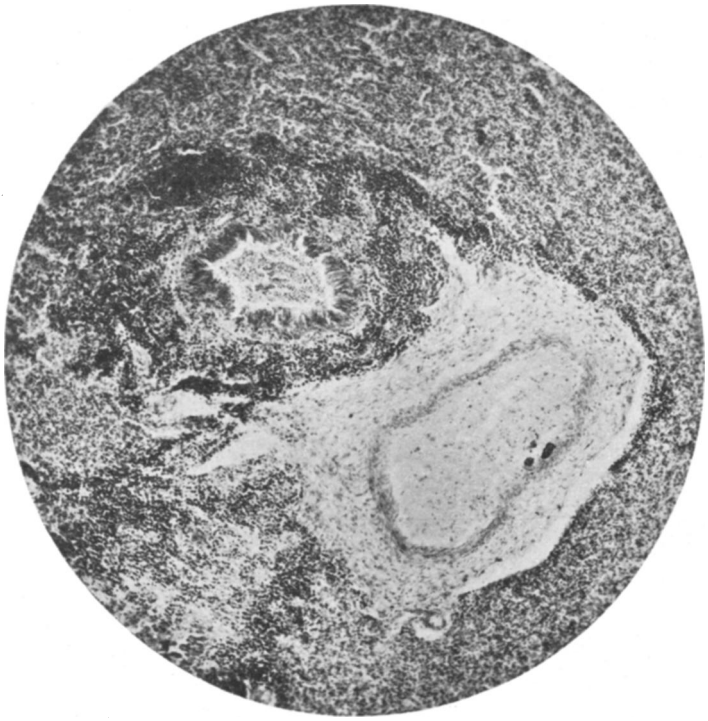

FIG. 1.—Photomicrograph showing the extensive plasma cell infiltration about the bronchial tubes.

Strikingly conspicuous, especially as shown by the methyl green-pyronin stain, is the extensive plasma cell infiltration in the walls of the bronchi (Fig. 1). This is seen both in the large and small bronchi and appears to be chiefly in the peribronchial lymph spaces. About some of the bronchi the exudate consists of plasma cells almost entirely, the small mononuclear and polynuclear cells being but few. Plasma cells occur also in the connective tissue spaces about small blood vessels, and, as stated, may be seen in the

epithelium. They may be found free in the bronchial lumen[1] and in abundance about the larger blood vessels in the region of the bronchi and along the fibrous septa in the lymph channels. Evidently they do not wander into the alveoli for they are not found here. In one case in which there was clinical evidence of bronchopneumonia for a few days only and in which consolidation was not extensive, the plasma cells about the bronchi are present in moderate numbers only.

The alveolar walls are congested and here and there is desquamation of the lining cells of the alveoli. In one case there are in the alveoli a few giant cells evidently formed from the desquamating epithelium.

The exudate in the bronchi and alveoli contains, as a rule, many polynuclear leukocytes; in places, indeed, there seems to be little else. In the larger bronchi, in addition to the numerous pus cells, a few plasma cells, as already stated, may be seen at times. Desquamated epithelial cells are not uncommon, also other mononuclear cells. The latter are probably what Mallory has called mononuclear leukocytes and which were found so commonly by Councilman, Mallory, and Pearce in bronchopneumonia in diphtheria. In the early stages, as was noted especially in one case, there is in the larger bronchi an abundance of tenacious mucoid secretion which, in smears, reveals mucinous material with numerous leukocytes and influenza bacilli. In the alveoli, as stated, polynuclear leukocytes are the chief cellular elements. Plasma cells are practically never found here, but mononuclear cells may be moderately abundant at times. Large, swollen, desquamated epithelial cells containing brown or nearly black pigment are found almost constantly. In some parts of the lung, especially those bordering on the involved regions, these large cells may be very numerous and frequently contain many ingested polynuclear and mononuclear cells. They often show evidence of fatty degeneration.

The occurrence of fibrin in influenzal pneumonia has been the subject of numerous remarks in the literature. Some authors state

[1] That plasma cells may migrate through tissues, epithelium, etc ., has been shown by Schridde, *Fol. haematologica*, 1907, Supplement, 3, p. 286.

that the fibrin is absent or occurs in small amounts only. Others report finding it in large amounts especially in the mixed or cellular-fibrinous type. In the cases here examined fibrin is found in all, but on the whole it is not abundant. Its distribution in the tissues is limited almost entirely to the alveoli immediately around the larger bronchi, where it occurs in rather large masses in the centers of the distended alveoli. Occasionally an isolated mass is seen in the lung tissue at some distance from a bronchus, especially in the newly involved portions. In the bronchi it is often seen in considerable quantities covering the epithelium and appears here, as a rule, as a fine meshwork and not as solid hyaline masses.

Red blood corpuscles are commonly found in the bronchi and in the alveoli, especially near bronchi where fibrin is abundant. Nowhere are definite hemorrhages seen. In the vessels not infrequently are thrombi of considerable size, partly or entirely occluding the lumen. The vessel walls are not involved and no changes except swelling of the endothelial cells lining the arteries are seen. Often in the lumen of the smaller vessels are masses of cells, many mononuclear but chiefly polynuclear in type, which are sometimes imbedded in fibrin.

The interstitial tissue shows some cellular infiltration in places, though not to an extensive degree. As stated, plasma cells are found in abundance along the connective tissue septa. Here and there, especially under the pleura, may be seen accumulations of round and polynuclear cells in the lymph channels. No increase in connective tissue appears in the septa, pleura, or in the alveolar walls. Beginning organization was noted in one case in the exudate in a small bronchus.

BACTERIOLOGY.

The influenza bacillus was found in pure culture in the heart's blood in three cases. Smears of the bronchial and lung exudate, sections of the lung tissue suitably stained, and cultures on blood media were examined with reference to bacteria. Generally the influenza bacillus was found as the predominating organism. In one case invasion of the lung by saprophytes after death had occurred to such an extent that pure influenzal cultures were not obtained, but in the smears many typical influenza bacilli were

seen. A few pneumococci or streptococci and at times both were found in the bronchi and lung exudates in culture, and in the stained sections cocci were often seen mixed with the bacilli. This is not surprising in view of the fact that these organisms are constantly found in the mouth, throat, and sputum and may easily be inhaled into the lung tissue. Their insignificant numbers and the general preponderance of influenza bacilli make it appear very improbable that they played any important part in the process. They were undoubtedly secondary invaders and have as much or as little significance as the not uncommon finding of a few streptococci or influenza bacilli in the lung exudate in lobar pneumonia.

In the sections stained with Giemsa stain immense numbers of bacilli were often seen in the leukocytes, especially in the bronchi. They were much less commonly found in the alveoli. Coccus forms also were seen in such preparations, confirming the results obtained by cultures. Occasionally there occurred in the bronchi masses of small bacilli staining blue in the hematoxylin preparations. I was never able to see influenza bacilli in the epithelial cells as has been reported by some observers.

In view of these results, it would seem that in the larger bronchi the process is generally limited to an inflammation of the mucosa and peribronchial tissue with little involvement of surrounding alveoli. It is in the smaller bronchi, however, that the process appears most intense. Here is seen in every case extensive peribronchial cellular infiltration, chiefly of plasma cells, a fact which points to these parts of the bronchial tree as being the chief seat of infection. Undoubtedly the influenzal infection in these cases which began as "colds" passed down the respiratory tract, localizing in these smaller bronchi and existing for a time as a bronchitis and peribronchitis. It later extended farther along the tubes and also laterally into the adjacent alveoli (chiefly the former), producing the well marked lobular pneumonia.

A review of the literature shows that pneumonia often has been found associated with influenzal meningitis. The lesions have not, however, been very carefully described, and usually the mere statement of an associated bronchopneumonia appears in the reports. At the present time 60 cases of influenzal meningitis have

been reported, and autopsies have been made in about one-half of this number. I have reviewed the records of 26 cases in which statements appear concerning the condition of the lungs, and in 20 there was found lobular pneumonia. Lobar pneumonia was not found in any. So far as the descriptions indicate, there seems to be a striking similarity in all. Ghon[1] describes concisely the lesions in one of his cases as follows: "In both lower lobes are scattered, elevated, pea-sized, nodular, grey-red, air-free regions. In the bronchi is a mucopurulent secretion and the mucosa is red and swollen." In his second case the lobular pneumonia was confluent in places. Microscopically the alterations were those of ordinary bronchopneumonia. Leukocytes were abundant and some fibrin was present. In the centers of the nodules was often some dissolution of alveolar septa. The reports on the bacteria found in the lungs are also usually incomplete. Cultures were made in only a few cases and the statements are mostly based on observations of microscopic sections. Generally small bacilli (influenza), intracellular and extracellular, have been found mixed with cocci, usually streptococci. In general the above statements apply to all the cases in the literature so far as the records permit one to say. They are also in complete accord with the cases described in this paper.

The most complete accounts of the pathology of pneumonias occurring in the ordinary acute respiratory form of influenza have been given by Pfeiffer,[2] Beck,[3] and Leichtenstern.[4] The type that seems to occur frequently and in which Pfeiffer especially found influenza bacilli, pure or nearly pure, in the lung parenchyma, is that of a catarrhal bronchopneumonia. As stated, mixed forms and lobar pneumonia are at times common during epidemics of influenza, but the authors cited claim they are usually if not always due to mixed infections. According to their descriptions of influenzal bronchopneumonia the lung surface has a mottled, light-gray and flesh-red color and shows little or no fibrin. The lobular pneumonic regions may be found in all lobes but occur more fre-

[1] *Wien. klin. Wchnschr.*, 1902, 15, p. 667.

[2] *Ztschr. f. Hyg. u. Infektionskr.*, 1893, 13, p. 357.

[3] Kolle and Wassermann, *Handbuch der Path. Microorg.*, 3, p. 382.

[4] Nothnagel, *Spec. Path. u. Therapie.*, 4, p. 83.

quently in the lower, and the bronchi are filled with thick pus in which the influenza bacilli, often mixed with cocci, are numerous. Round cell infiltration is common about the bronchi and in the alveolar walls. Beck states that the catarrhal process in influenza advances down the passages in a branching manner, thus producing the lobular distribution. Comparing the description of this type of pneumonia, especially as given by Pfeiffer, with the pneumonia encountered in the meningitis cases, one must admit that no characteristic features exist which will differentiate them.

Lord[1] has also described a number of cases of influenza pneumonia which were confirmed by bacteriological studies and he likewise concludes that the influenza bacillus does not produce a definite or specific type of pneumonia.

I have assumed, heretofore, that the bacilli found in influenza meningitis and that found in true epidemic influenza are identical. Cohen[2] contends that there is evidence from conglutination and other tests to believe that they are not alike, and his results seem to have been confirmed recently by Odaira,[3] who made extensive agglutination and hemolytic experiments for differential purposes. However, morphologically and culturally they cannot be differentiated and it would appear from the study here made that they produce lung lesions which are indistinguishable from one another. If different at all, they are without doubt very closely related and I am inclined to believe that the difference noted by Cohen may be simply one of virulence.

Not only do the lobular lung lesions found in influenzal meningitis and in true influenza appear to be identical but they agree closely with the acute lobular pneumonia occurring commonly in children, especially during the course of various infectious diseases. The localization generally posteriorly and in the lower lobes, the lobular distribution, the nodular, at times confluent, elevated, consolidated regions, variable in size with adjacent small atelectatic areas, the cellular character of the exudate with its scant fibrin content, and the distribution of the bacteria all agree even in

[1] Osler, *Modern Medicine*, 2, p. 474.

[2] *Ann. de l'Inst. Pasteur*, 1909, 23, p. 273.

[3] *Centralbl. f. Bakt.*, 1, Orig., 1911, 61, p. 289.

minutest detail with our conception of acute catarrhal or lobular pneumonia as given in our standard textbooks.

In none of the cases of meningitis was the pneumonia associated with such complications as abscess formation, gangrene, extensive necrosis, hemorrhages, bronchiectasis, etc., as noted in influenza pneumonia by some authors.[1] This may be due to the fact that sufficient time did not elapse for such processes to go on, the patients dying relatively early from the meningitis. Bronchiectasis has been noted in chronic bronchopneumonias, especially following influenza, measles, and pertussis, in which conditions the influenza bacillus has often been found. Boggs[2] reports a series of such cases and Vogt[3] calls especial attention to this point. At times there was noted a breaking down of the walls of bronchioles and alveoli with accumulation of pus cells, disintegration and disappearance of the epithelium. Had the meningitis patients continued to live, it is possible that such processes might cause bronchiectatic cavities to form, but one would not expect to meet them in an acute condition.

A word might be said concerning the hypostatic paravertebral pneumonia as described by Gregor and later and more completely by Bartenstein and Tada.[4] This form of pneumonia, according to these authors, develops chiefly in the posterior and lower parts of the lung and results from circulatory disturbances which may have a variety of causes (form of breathing, malnutrition, etc.). Infection plays no etiological rôle whatever. Though bacteria are often found in the tissues, they are purely secondary invaders, as evidenced by the fact that in the very beginning of the process they are not found in small pneumonic regions nor in the advancing periphery of the larger ones. Another feature of paravertebral pneumonia is a general bloody and hyperemic condition of the lung tissues as contrasted with the more local hyperemia of the infective form. As regards the cases of influenzal pneumonia above described, marked hyperemia was not a striking feature, the tissue as a rule being grayish red. In sections the bacteria were found everywhere, being present in the margins of the consolidated por-

[1] Paltauf, *Wien. klin. Wchnschr.*, 1899, 12, p. 576.

[2] *Bull. Johns Hopkins Hosp.*, 1905, 16, p. 288.

[3] *Fortschr. d. Deutsch. Klin.*, 1911, p. 473.

[4] *Beiträge zur Lungenpathologie der Säuglinge*, Leipzig, 1907.

tions as well as in the bronchial exudate. Again, the bronchi are intensely and probably primarily involved in these cases, as shown by the marked peribronchial infiltration, whereas in the paravertebral form the parenchyma is first involved and only later are the bronchi affected. For these reasons I think it is evident that influenzal pneumonia does not belong to the hypostatic paravertebral type.

SUMMARY.

Influenzal bronchopneumonia occurs in a large proportion (78 per cent) of all cases dying of influenzal meningitis. As a rule it develops early and may precede the appearance of the meningeal symptoms.

The influenza bacilli are found in the lung and bronchial exudate but usually mixed with a smaller number of other organisms (streptococci, pneumococci, etc.). The lungs are probably the atrium of infection in many cases though not in all.

The pneumonia is always lobular in character and does not appear to differ morphologically in any essential respect from the lobular pneumonia commonly associated with the respiratory type of influenza or from that associated with other acute infectious diseases.